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Assessing Pain in Patients With Polycystic Kidney Disease: Opportunities, Challenges, and Insights

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and is associated with various clinical manifestations. The natural history of ADPKD is associated with early hypertension, gradual kidney and liver enlargement, and an increased risk of intracranial aneurisms.[1] Progressive alteration of kidney function leads to end-stage kidney disease, requiring dialysis and/or kidney transplantation. Intracranial aneurisms are usually nonsymptomatic but can rupture, leading to subarachnoid hemorrhage and death. Most observational and interventional studies on ADPKD have focused on screening and interventions aiming at reducing the risk of surrogate outcomes, including kidney function decline,[2] kidney and liver volume enlargement,[3] and intracranial aneurisms.[4] Although these surrogate outcomes are likely to be associated with patient-centered outcomes such as survival, end-stage kidney disease, and pain, clinical and patient-reported outcomes are less often reported than surrogate outcomes in clinical trials.[5]

Pain affects more than 60% of patients with ADPKD, and often leads to the diagnosis of the disease.[6] Tolvaptan, a vasopressin type 2 receptor antagonist, has shown efficacy in reducing the growth of total kidney volume and kidney disease progression in patients with ADPKD.[2] In the TEMPO randomized trial,[2] kidney pain was identified as more common in the placebo group (35% of participants) than in the tolvaptan group (27%). Octreotide, a long-acting somatostatin analogue, has not been shown to reduce the decline in estimated glomerular filtration rate in patients with ADPKD;[3] however, it is associated with a decrease in the rate of kidney and liver enlargement.[3] Bodily pain, measured using SF-36, a non-ADPKD–specific health-related quality-of-life questionnaire, was lower in patients treated with octreotide, compared with patients who were given placebo. Therefore, interventions reducing the total kidney volume growth rate, a surrogate outcome, in patients with ADPKD, may be associated with an improvement of patient-reported outcomes. Nevertheless, pain is rarely and inconsistently reported in clinical trials,[5] which may explain why current recommendations regarding the use of tolvaptan in ADPKD are based on age, estimated glomerular filtration ratedecline, and total kidney volume, but do not include pain in the treatment algorithm.[7]

Considering that pain is subjective, it requires to be assessed using a patient-reported outcome measure. Lack of pain reporting in clinical trials is likely because of the difficulties in assessing pain reliably. To improve the consistency of pain reporting in studies, the international standardized outcomes in nephrology—polycystic kidney disease (SONG-PKD) initiative has developed a specific instrument, the SONG-PKD Pain measure, that aims to constitute a core outcome measure that can be implemented in clinical trials and used in clinical practice.

In their study, Cazzolli *et al.* report the psychometric properties of the SONG-PKD Pain measure classic test theory.[8] The SONG-PKD Pain measure is a short questionnaire, consisting of 3 questions aiming at assessing the frequency, intensity, and impact of PKD-related pain within the past week, using a 5-point Likert scale. The obtained score varies from 0 to 12 (highest pain). The authors demonstrate good psychometric properties of the SONG-PKD Pain measure with good convergence

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with other pain instruments that are less adequate to evaluate pain in patients with ADPKD and show a high level of internal consistency and stability.

The SONG-PKD Pain measure validation study,[8] however, was with challenges. Although the development of the SONG-PKD followed the COSMIN guideline process—including a literature review and a multistakeholder workshop to select the most relevant dimensions of pain—the relevance of these choices warrants further consideration. The systematic review[9] on which the development of the SONG-PKD is based identified the following 4 key content dimensions of pain: site of pain, measurement (intensity, frequency, temporality, and sensory characteristics), type (nociceptive and neuropathic), and impact (on life participation, sleep, and mental health). Among these, the SONG-PKD investigates 3 dimensions, namely frequency, severity, and impact on life participation. Although these choices appear coherent, it is crucial to question whether they sufficiently capture the multifaceted nature of pain in this context. The issue of content validity remains open to further scrutiny. Moreover, the authors assign equal weight to each dimension in estimating the overall pain score, a methodological choice that raises questions about its appropriateness for accurately reflecting the complexity of pain.

Although the estimated sample size required for the study was 450, only 358 participants were enrolled. Given that the authors were not able to determine the reason for noncompletion of the questionnaire and for nonparticipation in the study, it is possible

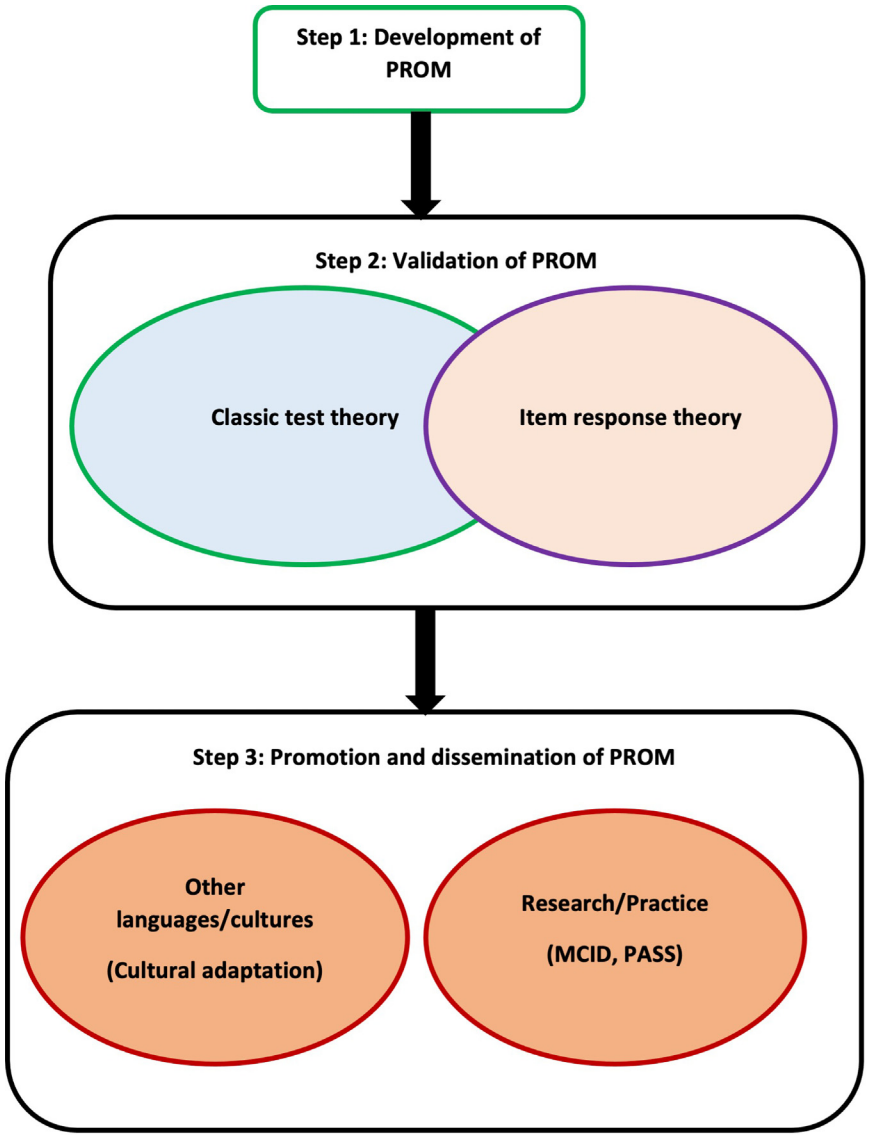

Figure 1. Logical steps for the development and dissemination of a patient-reported outcome measurement. MCID, minimal clinically important difference; PASS, patient acceptable symptomatic state; PROM, patient-reported outcome measurement.

that the population that participated in the study and completed the questionnaire is not fully representative of the ADPKD population. Possible population selection bias is highlighted by the demographic characteristics of the study participants. Education level of the study participants was higher than the level of education in the general population: 70% of the participants received university training, whereas the percentage of people 25 and older with university training in the United States, where the majority of study participants resided, is approximately 63%.[S1] Participants were invited to participate in the study through email invitations, which might explain the selection of a highlyeducated population. Seventy percent of the study participants were females, and > 90% were White. Although the authors were able to show that the SONG-PKD Pain measure performed similarly between males and females,[8] other demographic subgroup analyses were not performed.

The development and validation of disease-specific patient-reported outcome measureinstruments and their use in clinical trials will improve the level of scientific evidence regarding the effect of interventions on patient-reported outcomes. It will help identify additional treatment indications aimed at improving the quality-of-life of patients with ADPKD and convince health authorities and the medical community of the necessity of proposing these interventions. The use of a patient-reported outcome measurein clinical practice can be particularly valuable when addressing a prevalent symptom in ADPKD, such as pain. Therefore, the development and validation by the SONG-PKD initiative of a disease-specific, reliable, reproducible, and easy to administer core outcome pain measure is a key step to improve the reporting of pain in clinical trial and thus, improve pain management in patients with ADPKD. Several steps remain necessary to achieve the effective implementation of the SONG-PKD pain questionnaire (Figure 1). First, psychometric validation through classical test theory does not adequately evaluate certain critical properties, such as unidimensionality, differential item functioning, and measurement invariance. Employing item response theory could address these gaps, enabling a more robust assessment of these characteristics and facilitating the definition of more appropriate item weighting for score calculations.

Second, promoting the broader use of this questionnaire requires its cultural adaptation to other languages and contexts. Culturally adapting the questionnaire ensures its relevance and applicability across diverse populations, which is vital for its global adoption.

Finally, for its application in clinical research and routine practice, establishing key indicators such as the Minimum Clinically Important Difference and the Patient Acceptable Symptomatic State is crucial.[S2,S3] These 2 concepts are essential for interpreting patient-reported outcome measure scores at the individual level. The minimum clinically important difference represents the smallest change in measurement that reflects a meaningful improvement or deterioration in symptoms. It is particularly valuable in clinical research, for example, to calculate sample sizes when pain is used as an outcome measure. The patient acceptable symptomatic state defines a symptom state that patients consider acceptable and serves as a practical guide for clinicians in treatment decisions.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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